
Transient inactivation of Rb and ARF yields regenerative cells from postmitotic mammalian muscle.

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Public Summary:

An outstanding biological question is why tissue regeneration in mammals is limited, whereas urodele amphibians and teleost fish regenerate major structures, largely by cell cycle reentry. Upon inactivation of Rb, proliferation of postmitotic urodele skeletal muscle is induced, whereas in mammalian muscle this mechanism does not exist. We postulated that a tumor suppressor present in mammals but absent in regenerative vertebrates, the Ink4a product ARF (alternative reading frame), is a regeneration suppressor. Concomitant inactivation of Arf and Rb led to mammalian muscle cell cycle reentry, loss of differentiation properties, and upregulation of cytokinetic machinery. Single postmitotic myocytes were isolated by laser micro-dissection-catapulting, and transient suppression of Arf and Rb yielded myoblast colonies that retained the ability to differentiate and fuse into myofibers upon transplantation in vivo. These results show that differentiation of mammalian cells is reversed by inactivation of Arf and Rb and support the hypothesis that Arf evolved at the expense of regeneration.

Scientific Abstract:

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